ELSEVIER

CrossMark

Magnetite nanoparticles for cancer diagnosis, treatment, and treatment monitoring: recent advances

Richard A. Revia and Miqin Zhang*

Department of Materials Science and Engineering, University of Washington, Seattle, WA 98195, USA

The development of nanoparticles (NPs) for use in all facets of oncological disease detection and therapy has shown great progress over the past two decades. NPs have been tailored for use as contrast enhancement agents for imaging, drug delivery vehicles, and most recently as a therapeutic component in initiating tumor cell death in magnetic and photonic ablation therapies. Of the many possible core constituents of NPs, such as gold, silver, carbon nanotubes, fullerenes, manganese oxide, lipids, micelles, etc., iron oxide (or magnetite) based NPs have been extensively investigated due to their excellent superparamagnetic, biocompatible, and biodegradable properties. This review addresses recent applications of magnetite NPs in diagnosis, treatment, and treatment monitoring of cancer. Finally, some views will be discussed concerning the toxicity and clinical translation of iron oxide NPs and the future outlook of NP development to facilitate multiple therapies in a single formulation for cancer theranostics.

Introduction

The development of nanoscale technologies has been widely touted as a revolutionary paradigm shift for detection and remediation of cancer. Indeed, the surge in research efforts exploring the design and synthesis of nanoparticle (NP) systems has seen the creation of many material formulations exhibiting promising therapeutic and diagnostic (theranostic) effects toward the treatment of various cancer types in a single nanodrug [1–3]. NP configurations include those with fundamental cores of organic molecules (e.g. dendrimers, DNA, lipids, viruses, and micelles), inorganic molecules (e.g. iron oxide, gold, quantum dots, carbon nanotubes, and fullerenes), or a hybrid of two or more of these components [4,5]. Each base structure has associated advantages and disadvantages that depend on the application under consideration. Furthermore, these formulations have properties that are tunable to some degree, such as size, surface charge, and hydrophobicity, allowing them to be optimized for a desired function.

Iron oxide NPs with nanocrystalline magnetite (Fe_3O_4) cores have great potential for use in oncological medicine due to their biocompatibility [6], biodegradability [7], facile synthesis [8], and ease with which they may be tuned and functionalized for specific applications. Additionally, spherical magnetite NPs with diameters less than approximately 20 nm will exhibit superparamagnetic behavior, a property that is exploited to enhance contrast in magnetic resonance imaging (MRI) [9–11]. Typically, superparamagnetic iron oxide nanoparticle (SPION) conjugates are comprised of a magnetite core providing inherent contrast for MRI and a biocompatible coating that provides ample functional groups for conjugation of additional tumor targeting and therapeutic moieties. As some formulations of magnetite-based NPs have already gained approval for use in humans as iron deficiency therapeutics and as MRI contrast agents by the Food and Drug Administration (FDA) (e.g. Feraheme®, Feridex I.V.®, and Gastromark®), extension of these NP configurations for uses beyond MRI contrast enhancers such as cancer therapeutics via drug delivery, biotherapeutic transport, magnetic hyperthermia, photothermal ablation, and photodynamic therapy (PDT) may be fast-tracked as compared to NP formulations lacking widespread acceptance of nontoxicity (e.g. other metal-core NPs) [11]. This idea highlights the considerable capacity iron oxide NPs have for use in highly personalized medicine; as researchers develop a library of synthesis protocols and discrete nanoscale modules with specific roles for

*Corresponding author: Zhang, M. (mzhang@uw.edu)

1369-7021/© 2015 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). http://dx.doi.org/10.1016/j.mattod.2015.08.022

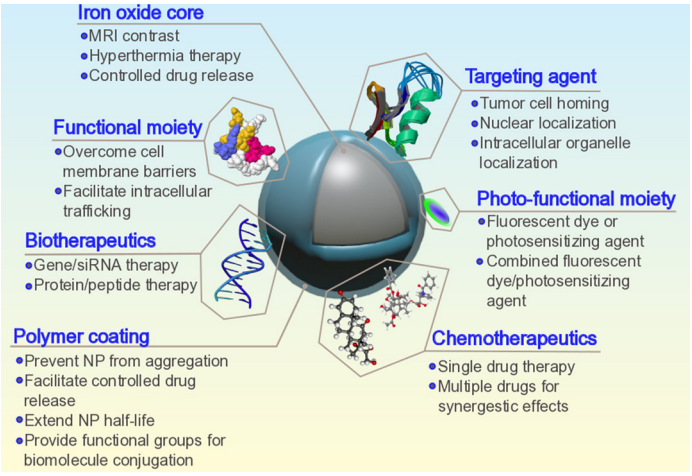

FIGURE 1

Schematic illustration of a full-suite theranostic NP. The magnetite core serves as an MRI contrast agent and heat source for magnetic hyperthermia, and a polymer coating increases biocompatibility, mitigates RES uptake, and allows for facile functionalization with chemotherapeutic, biotherapeutic, optical enhancement, and targeting moieties.

cancer theranostics, individualized NP formulations exhibiting a full-suite of treatment and diagnostic capabilities may be created in an efficient and effective manner. An exemplary NP incorporating a multitude of diagnostic and therapeutic features is depicted in Fig. 1.

There are a few reviews focusing on the development and applications of magnetite NPs [12–16]; this article aims to provide an update of new findings emergent in the field since 2013. This review discusses recent advances in employing iron oxide-core NPs for diagnosing and monitoring cancer through imaging modalities, the treatment of tumors via transportation of chemotherapeutic and biotherapeutic agents (i.e. drugs, nucleic acids, and proteins), magnetic hyperthermia and photothermal therapies, as well as PDT. Finally, overviews of the new concept of NanoEL, nanotoxicity of metal-oxide NPs, and some remarks regarding the translation of nanotherapeutics into a clinical setting are provided.

SPIONs in cancer diagnosis and treatment monitoring

Imaging tumorous tissue is of paramount importance in the diagnosis and treatment monitoring of cancer [17,18]. Clear depictions of tumor boundaries allow for accurate judgments of tumor distribution and its response to surgical removal and adjuvant therapies. Many imaging modalities are employed for early detection and interrogation of cancer, including X-ray, ultrasound, MRI, computed tomography (CT), and positron-emission tomography (PET) [17]. Iron oxide NPs have been extensively researched for their use in augmenting contrast for MRI [19]; recently, hybrid NP formulations with superparamagnetic iron oxide cores modified with exterior coatings and functional probes have been devised for their ability to enhance contrast in alternative imaging techniques in addition to MRI.

Contrast enhancing NPs that can selectively accumulate at tumor sites help to provide precise information regarding tumor extent. The method of NP accumulation at tumor sites is typically categorized into two separate classes: passive and active targeting. Passive targeting relies on the enhanced permeability and retention (EPR) effect [20]. A hallmark of cancerous tissue is the formation of a perforated vasculature and maladroit intratumoral lymphatic drainage. NPs less than approximately 100 nm can pass through such leaky vessels into the tumor microenvironment and remain for an amount of time that is significantly longer than the blood clearance of the NPs; this is the EPR effect [21]. Passive targeting is limited however because not all tumors exhibit the EPR effect and the degree of permeability of the tumor vasculature is unlikely to be homogenous across the whole site [22]. Attempts at overcoming these limitations are made with active targeting. Active targeting is achieved by modifying an NP through the attachment of targeting ligands to the NP surface. Ligands that recognize biological structures unique to or overexpressed in cancer cells can then preferentially accumulate at tumor sites. A third mode of targeting unique to magnetic NPs such as SPIONs is the use of an external magnetic field to draw the NPs to the site of action [23]. All three of these targeting mechanisms are presently being employed in the development of SPIONs as imaging agents. The vast majority of SPION formulations are in preclinical development, although there are a number of studies using the iron oxide NP ferumoxytol as an MRI contrast agent currently undergoing clinical trials [24–27].

Recently, it was shown that iron oxide NPs as well as other NP formulations, induce gaps tens of microns in size between endothelial cells (i.e. cells that form the interior walls of blood vessels) [28,29]. The mechanism by which NPs cause such openings was dubbed nanoparticle-induced endothelial leakiness (NanoEL) [30,31]. Prior to the discovery of NanoEL, the routes for NPs to escape the endothelium were thought to be confined to typical transcellular endocytosis and diffusional transport through cell membranes via cell–cell junctions; however, these methods of NP transport through the endothelium alone are not sufficient to explain the speed with which NPs have been shown to enter certain highly vascularized organs like kidneys, liver, and spleen [30]. NanoEL occurs much more rapidly than either endocytosis or diffusion through cell–cell junctions. The phenomenon of NanoEL is described by the intracellular binding of NPs to VE-cadherin; following this pairing, phosphorylation of VE-cadherin is triggered which in turn results in a rearrangement of the endothelial cell cytoskeleton [32]. This insight into the interaction of NPs with biological environments is of paramount importance as it may provide an explanation for the physical mechanism by which off-target accumulation of NPs at sites other than tumors happens. Further exploration into how specific NP characteristics like size and surface charge alter the behavior of the NanoEL effect may help nanotechnologists to mitigate off-target NP accumulation and even exploit induced endothelial leakiness for therapeutic effects.

Magnetic resonance imaging

MRI is an immensely important tool in medicine offering detailed spatial resolution and soft tissue contrast without the use of ionizing radiation or potentially harmful radiotracers [33,34]. In MRI, a large external magnetic field is applied to a sample of interest resulting in an alignment of the magnetic moments of the protons within the sample. When SPIONs are present in such a system, their magnetic moments couple with the magnetic moments of nearby protons causing spin dephasing and a shortening of the relaxation times of protons in the vicinity [35].

Download English Version:

https://daneshyari.com/en/article/811675

Download Persian Version:

https://daneshyari.com/article/811675

Daneshyari.com